TO: OFFICE OF GRANTS AND RESEARCH CONTRACTS, NATIONAL AERONAUTICS AND SPACE ADMINISTRATION, Att. Code SC.

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A. The principal objectives of this study have been achieved, following an initial period of major difficulties with instrumentation which delayed commencement of work until December 10, 1966 (see Semi-annual Report of February 1).

B. We have studied a series of fifty cardiovascular-normal men in a narrow age range (22-35 years) utilizing the various measurements of cardiovascular function detailed in our proposal. Fifty-six men in all were studied in order to obtain fifty with technically acceptable results.

C. Important indices of cardiovascular function were calculated, usually by more than one computation and based on more than one type of cardiographic method as indicated below. In the case of Left Ventricular Ejection Period (LVET), we were quickly able to establish the optimum method, in agreement with both the indirect and direct measurements made by other groups. In several of the other indices, notably Isovolumetric Contraction Period (IVCT), widely conflicting reports based on different methods of measurement are extant. We are still in the process of writing papers on these detailing our results and explaining our preferences.

D. Our paper on Left Ventricular Ejection Time has been accepted for presentation at the International Congress of Angiology in Barcelona in September. However, lack of travel funds will not permit its presentation. It should appear in the Proceedings of the Congress.

A paper based on this work is about to be offered for publication.

E. Specific Results.

1. Left Ventricular Ejection Period (LVET).

LVET was measured by four different computations based on the published observations of other groups both in the U.S. and abroad. These included: the interval from beginning of the Carotid arterial pulse to its incisura --

$$LVET = CARu - In \qquad (1).$$

The interval from the maximal systolic peak of the Apexcardiogram (E) to the aortic component of the second heart sound -

$$LVET = E - II_A \qquad (2).$$

The interval in equation (2) with correction of the E-point by subtraction of the Carotid pulse transmission time (PPT)

$$LVET = (E \text{ minus } PTT) - II_A \qquad (3).$$

The interval in equation (2) with correction of the E-point by substitution of a preceding point on the ACG held by some investigators to represent the actual E (ejection) point

$$LVET = \text{"true E"} - II_a \qquad (4).$$

The composite results are given in Table I:

TABLE I

LEFT VENTRICULAR EJECTION PERIOD

<u>Results of Calculation by Different Methods</u>

METHOD	(1)	(2)	(3)	(4)
	CARu - In	E - II_A	(E - PTT) - II_A	"true E" - II_A
Range (msec)	240-320	120-330	160-350	250-350
mean	292	267	291	295
S.D. $\pm$	19	35	29	34
Correlation with method (1) r =	=	.502	.676	.525

Contrary to the impression gained from the first few patients (and noted in the semi-annual report), results with equation (1) were virtually identical with those of other workers using this measurement and entirely comparable to the sparse reports of directly measured LVET using analogous points on the aortic curve. Moreover, LVET varied with heart rate in quite the same manner; for this our regression equation is:

$$y = 0.376 - 0.122\ x,$$

where y = LVET in milliseconds and x = heart rate in beats per minute.

While the other methods --- equations (3) and (4) especially --- yielded mean values in the same range, they were rejected for further use because: (a) the points measured are technically clearer in method (1); (b) method (1) reflects both in technique and results the direct measurement from catheterization of the aorta; and (c) the correlation coefficients with method (1) were much too low. (See Table I)

2. <u>Left Ventricular Isovolumetric Contraction Period (IVCT).</u>

IVCT is a period of great physiologic importance for which the end-point is agreed: beginning of ejection. However, its beginning is subject to varying interpretation. Consequently, we have calculated this by six different methods. (Two additional calculations have been completely rejected because they involve the "true ejection" point of the ACG described above under LVET; since this point is often difficult to establish and, in any event yields unacceptable results for LVET, we have eliminated it from further consideration). The beginning of IVCT is reckoned either from (a) closure of the Mitral Valve, from (b) the beginning of the Left

Ventricular pressure rise (now known to precede Mitral Valve closure), or from (c) the first detectable movement of the Left Ventricle. Of these, (b) can only be detected by catheterization or direct heart puncture at operation --- procedures during which the patient cannot be physiologically "normal" owing to the trauma of the procedure and/or accompanying anesthesia or sedative medications. Closure of the mitral valve can be detected approximately either by these direct methods or by phonocardio- graphy ~~logy~~, represented by the "mitral closure" sound --- the first rapid vibrations of the First Heart Sound. The earliest Left Ventricular movement (c) can only be detected by external methods; we have used the Apexcardiogram for this.

The following calculations, all sanctioned by various reports in the literature, have been used:

Interval from beginning of the Apexcardiogram (ACGu) to beginning of the Carotid arterial pulse:

$$IVCT = ACGu - CARu \qquad (1).$$

Interval above corrected for Pulse Transmission Time (PPT):

$$IVCT = ACGu - (CARu \text{ minus } PPT) \qquad (2).$$

Interval between ACGu and the E-point of the ACG:

$$IVCT = ACGu - E \qquad (3).$$

Interval from the "mitral closure" sound I_M and the E-point:

$$IVCT = I_M - E \qquad (4).$$

Interval between mitral closure and beginning of the Carotid arterial pulse:

$$IVCT = I_M - CARu \qquad (5).$$

Interval above corrected for Pulse Transmission Time:

$$IVCT = I_M - (CARu \text{ minus } PTT) \quad (6).$$

The composite results are given in Table II.

These results find their counterparts in other reported work, with the exception of Equation (2), in which we have the most confidence. We are preparing a report giving all of this work and stating our reasons for preferring Equation (2), Briefly, these include the reliability of the points measured, the necessity of allowing for Pulse Transmission delay, and the necessity of considering Left Ventricular movement from its very earliest detectable instant. At present the latter is only possible with the Apexcardiogram and we have shown that this even precedes the "Initial Ventricular Movement" of the Kinetocardiogram (KCG) by a mean value of about 16 milliseconds. The latter is reflected in our figures for the Electromechanical Lag noted below.

3. <u>Electromechanical Lag (Electromechanical Interval; EMI)</u>

This period represents the time from electric stimulation of the myocardium to its mechanical response. Its physiologic importance is not completely understood and we propose to study this in association with the continuation of this work. This has been customarily measured by many investigators by the time from the onset of electric activity (q of the Electrocardiogram) to the first rapid vibrations of the first heart sound

TABLE II

ISOVOLUMETRIC CONTRACTION PERIOD OF THE LEFT VENTRICLE

Comparison of Methods of Measurement

	(1)	(2)	(3)	(4)	(5)	(6)
METHOD	ACGu - CARu	(1) corrected for PPT	ACGu - E	I_M - E	I_M - CARu	(5) corrected for P.
Range (msec)	70 -120	40-90	30 - 200	20 - 140	40 - 100	10 - 70
Mean	94.1	70.9	97.4	58.6	61.8	39.0
S.D.	13.9	15.8	29.6	25.2	14.0	13.9
S.E.	2.1	2.4	4.2	3.6	2.0	2.0

(I_M). We have repeated this measurement, but, in agreement with newer work, we consider the beginning of the Apexcardiogram as more reliable since, clearly, mechanical activity begins well before mitral valve closure. As expected, The differences between these results are quite large:

TABLE III

ELECTROMECHANICAL INTERVAL OF THE LEFT VENTRICLE

METHOD	$q - I_M$	q - ACGu
Range (msec)	30 -70	00 - 50
Mean	50.2	22.6
S. D.	13.0	9.8
S. E.	1.9	1.4

4. Tension Period

This interval, considerably investigated in Europe, remains of uncertain significance, since it comprises both Electromechanical Lag and Isovolumetric Contraction. We have measured it by the three methods shown in Table IV (symbols = same abbreviations as heretofore). We shall include this in our studies of behavior of the heart under various stresses to see if information of physiologic value is forthcoming. At this point, it appears that evaluation of its component intervals is more justifiable. Of the methods used (Table IV), method (3) is derived from an endpoint in which we have greater technical and physiologic confidence.

5. Isometric Relaxation Period

Isometric Relaxation Period (IRP) has physiologic meaning comparable to that of the Isovolumetric Contraction Period, although it may vary in a

TABLE IV

TENSION PERIOD OF THE LEFT VENTRICLE

	(1)	(2)	(3)
METHOD	q - E	q - CARu	q - (CARu minus PPT)
Range (msec)	80 - 200	90 - 150	70 - 140
mean	120	118	95
S.D.	25.4	14.4	25.9
S.E.	3.6	2.0	3.7

different manner under the same circumstances. We have measured this by the single generally accepted technique for atraumatic measurement: the time from aortic valve closure (as indicated by the Aortic sound: II_A) to that of mitral valve opening (as reflected in the O -point of the apexcardiogram, yielding the following results:

TABLE V

ISOMETRIC RELAXATION PERIOD OF LEFT VENTRICLE

METHOD	II_A - O
Range (msec)	40 - 100
mean	67.0
S.D.	14.6
S.E.	2.1

Other work on this period in normal people is quite sparse. Ours appears to be a lower figure than reported elsewhere, but other series have not been entirely male and have not been in such a narrow age range. Moreover, most other subjects have been "hospital normals" rather than fully active "non-patients". Because of our confidence in the technical accuracy of our measurements, we feel that this is the explanation for any discrepancy.

6. <u>Rapid Filling Period</u>

This interval (RFP) is measured from the "O" point of the Apexcardiogram to the end of the Rapid Filling Wave of the same record. This yielded the following results:

TABLE VI

RAPID FILLING PERIOD OF THE LEFT VENTRICLE

METHOD	0 - end RFW
Range (msec)	80 - 120
mean	99.8
S.D.	14.2
S.E.	2.1

F. A mass of data on individual points of measurement of each of the individual curves reflecting cardiac activity remains to be submitted for statistical analysis. This is not in the "direct line" of our efforts and we have postponed this until we can digest the far more significant results detailed in this report. Finally, we have not been able to get reliable data for the Isometric Relaxation Period of the Right Ventricle owing to unacceptable variation in the time of the v - wave of the Jugular Venous Pulse recording. We have data on the Slow Filling Period of the Left Ventricle, but this appears to be purely a function of cardiac rate and of no consequence in normal individuals.

G. SUMMARY AND CONCLUSIONS

Significant intervals of left ventricular function have been studied by external, atraumatic methods, including a comparison of several techniques of measurement.

Numerical data are summarized in Tables I to VI.

Reasons for preferring one or another calculation are stated where there are varying results.

Because of the voluminous international literature bearing directly --- or, more frequently, indirectly --- on this work, evaluation is continuing beyond the end of the grant period. (We have received from the MEDLARS program of the Public Health Service 500 of 1081 citations from the literature for the period January 1964 through July 1967 alone, in addition to our own collection on this wide range of subjects).

A paper on Left Ventricular Ejection Period was accepted for presentation at the International Congress of Angiology. Another paperbased on this work is about to be presented for publication.

A paper on Isovolumetric Contraction Period of the Left Ventricle is in preparation, covering the points noted above with full discussion of our results and our point of view vis - a - vis the definition of this period in physiologically valid terms.

Papers on each if the other intervals will be prepared, giving our results and discussion as soon as we can fully digest the very disparate literature available.